REMARKS

This paper is being contemporaneously filed with a Petition for a three month extension of time and an authorization to debit Deposit Account No. 50-1275 for the appropriate fees. Claims 1-14, 29-31, 33-39, 45-49, and 53 are pending in this application.

Claim rejections under 35 U.S.C. § 102

Rejection over Kende et al.

Claims 1-14, 29-31, and 33-39 stand rejected under 35 U.S.C. § 102 as allegedly being anticipated by Kende et al. Kende et al. teaches a method of making alpha-ester sulfones. The disclosure of Kende et al., however, does not teach or suggest hydroxamic acid derivatives or methods of making them. Claim 1 has been amended to claim a method of preparing hydroxamic acid derivatives of formula I using a compound of formula V. Because Kende et al. does not teach or suggest methods of preparing hydroxamic acid derivatives, Applicants respectfully assert that independent claim 1, as amended, and claims 2-14, 29-31 and 33-39, which depend directly or indirectly therefrom, are not anticipated by Kende et al. Accordingly, Applicants request withdrawal of the rejection of claims 1-14, 29-31 and 33-39.

Rejection over WO00/44723

Claims 1-14, 29-31, 33-39 and 45-53 stand rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by WO00/44723. The international publication date for WO00/44723 is August 3, 2000. The present application claims priority to Provisional Application No. 60/226,312, filed January 27, 2000. Thus, WO00/44723 is not a proper reference under 35 U.S.C. § 102(b), since it was not published more than one year prior to Applicants' filing date. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(b).

Claim rejections under 35 U.S.C. § 112

Claims 1-14, 29-31, 33-39, and 45-53 stand rejected under 35 USC § 112, first paragraph, for allegedly lacking enablement. The Office Action correctly sets forth the Wands factors in addressing the enablement issue. The action indicates that the specification does not reasonably enable one skilled in the art to make compounds other than those where R_1 and R_2 form a piperidine ring, and where Z is CH_3-CH_2-O-, OH-NH-, -OH, or CH_3-O-, and where R_3 is phenyl, indicating the claims are overly broad. Applicants respectfully direct the Examiner's attention to page 24 of the specification as originally filed, which acknowledges that the methods depicted in the various schemes are limited to certain substituents (as noted in the Action) but that "additional compounds of this invention can be prepared in the same manner using the appropriate starting materials and routes, as would be appreciated by one skilled in the art." Pages 31-72 of the specification as originally filed contain specific examples of compounds made according to the claimed methods. However, these exemplary compounds and syntheses are just that: exemplary. Applicants respectfully direct the Examiner's attention to pages 23-30 of the specification as originally filed, which describe general methods for the preparation of compounds of the invention, including compounds other than those in the Examples. With respect to the state of the prior art and the skill of those skilled in the art, the Kende et al. reference discussed above, while lacking any disclosure of how to make hydroxamic acid derivatives, does provide insight on how to make compounds of formula V, providing particular examples where R_1 and R_2 do *not* form a piperidine ring. Thus, the Office itself has provided an example of the state of the prior art that suggests Applicants' invention is enabled. Given the schemes and direction provided in the specification, the state of the prior art

and the relative skill of those of skill in the art, Applicants assert that the full range of their claimed invention is fully enabled .

Applicants respectfully submit that their teachings coupled with the knowledge of those skilled in the art would fully enable one of skill in the art to make and use the full scope of Applicants' claims to methods of making the hydroxamic acid derivatives. Accordingly, Applicants respectfully request withdrawal of the rejection of claims 1-14, 29-31, 33-39, 45-47 and 53.

Claims 48 and 49 are rejected under 35 USC § 112, first paragraph, for allegedly failing to provide enablement for treating any disease or condition. Claims 48 and 49 are directed to methods of inhibiting pathological changes mediated by TNF-alpha converting enzymes (TACE). The Office appears to imply that clinical data on effectiveness is required for enablement under 35 USC § 112. Applicants respectfully submit that there is no such requirement under the enablement standard. The Action focuses on unpredictability, the need for clinical trials or other testing, and in vitro and in vivo testing to determine the pharmacological activities. While the FDA may require evidence of sufficient success rate and specific dosing patterns, there is no such requirement in the PTO. Applicants respectfully note that the criteria for attaining FDA approval of a drug are quite different than those used to determine enablement. See MPEP § 2164.05, citing *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

As discussed in prior responses, Claim 49 recites several specific disorders to be treated. As stated in prior responses, the art is replete with examples providing the nexus between TACE and many diseases/conditions. TNF-**α** is a pro-inflammatory cytokine that is believed to have a role in **rheumatoid arthritis** [Shire, M. G.; Muller, G. W. *Exp. Opin. Ther.*

Patents 1998, *8(5)*, 531; Grossman, J. M.; Brahn, E. *J. Women's Health* 1997, *6(6)*, 627; Isomaki, P.; Punnonen, J. *Ann. Med.* 1997, *29*, 499; Camussi, G.; Lupia, E. *Drugs*, 1998, *55(5),* 613], **septic shock** [Mathison, *et. al. J. Clin. Invest.* 1988, *81*, 1925; Miethke, *et. al. J. Exp. Med.* 1992, *175*, 91], **graft rejection** [Piguet, P. F.; Grau, G. E.; *et al. J. Exp. Med.* 1987, *166*, 1280], **cachexia** [Beutler, B.; Cerami, A. *Ann. Rev. Biochem.* 1988, *57*, 505], anorexia, **inflammation** [Ksontini, R.; MacKay, S. L. D.; Moldawer, L. L. *Arch. Surg.* 1998, *133*, 558], **congestive heart failure** [Packer, M. *Circulation*, 1995, *92(6),* 1379; Ferrari, R.; Bachetti, T.; et. al. *Circulation*, 1995, *92(6),* 1479], post-ischaemic reperfusion injury, **inflammatory disease of the central nervous system, inflammatory bowel disease, insulin resistance** [Hotamisligil, G. S.; Shargill, N. S.; Spiegelman, B. M.; *et. al. Science*, 1993, *259*, 87] and **HIV infection** [Peterson, P. K.; Gekker, G.; *et. al. J. Clin. Invest.* 1992, *89*, 574; Pallares-Trujillo, J.; Lopez-Soriano, F. J. Argiles, J. M. *Med. Res. Reviews*, 1995, *15 (6),* 533], in addition to its well-documented antitumor properties [Old, L. *Science*, 1985, *230*, 630].

The nexus between TACE and each of the specific disorders and conditions claimed in claim 49 is provided by the references listed above (and emphasized in bold), with the exception of fever, which it will readily be recognized often accompanies many of the other conditions and therefore can be similarly treated. Thus, those of skill in the art are aware of diseases or conditions brought about by pathological changes mediated by TACE, and therefore would readily recognize the nexus between TACE and such diseases and conditions.

The Action acknowledges that the present compounds inhibit TACE, but declares "inhibition does not equal treatment." However, as discussed above, 35 USC § 112, first paragraph, does not require clinical efficacy data in order to show enablement. The Action further states "there is no absolute predictability even in view of the seemingly high level of skill in the art." Applicants note that absolute predictability is *not* the standard for enablement.

Applicants have shown the claimed compounds are TACE inhibitors and that there is a nexus between TACE and the claimed diseases and conditions. Thus, although there cannot be absolute predictability, those of skill in the art would reasonably expect that the compounds of the invention would be useful for the treatment of the claimed disorders.

The Action further questions what success rate would make a particular compound "successful" and what dosage is required. Applicants respectfully direct the Examiner's attention to pages 73-75 of the specification as originally filed, which describes assays for determining the effectiveness of the compounds of the invention. Applicants also direct the Examiner's attention to pages 76-78 of the specification as originally filed, which describe pharmaceutical compositions and dosage forms of the compounds of the invention. Applicants note MPEP section 2163.01(c), which states "it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation." Based on Applicants' disclosure, one skilled in the art could make effective dosage forms of the compounds of the invention without undue experimentation. As noted above, questions of success rate and efficacy are more properly the domain of the FDA, not the PTO.

As noted in MPEP section 2164.04, "the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." Applicants respectfully submit that the Office has not met this burden. Accordingly, Applicants respectfully assert that they have described the subject matter of claims 48 and 49 sufficiently to reasonably convey they were in possession of the invention at the time of filing. Withdrawal of the rejection under 35 U.S.C. § 112 is respectfully requested.

The Commissioner is hereby authorized to charge any fee or underpayment thereof or credit any overpayment to deposit account no. 50-1275.

Early reconsideration and allowance of all pending claims is respectfully requested. The examiner is requested to contact the undersigned attorney if an interview, telephonic or personal, would facilitate allowance of the claims.

Respectfully submitted,

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